Novel Therapies for Type 2 Diabetes

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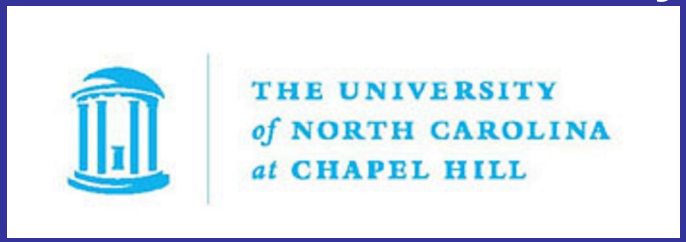

Overview

- GLP-1 receptor agonists
  - Exenatide (Byetta)
  - Liraglutide (Victoza)
- Amylin mimetics
  - Pramlintide (Symlin)
- Bile acid sequestrants
  - Colesevelam (Welchol)
- Dopamine agonists
  - Bromocriptine-QR (Cycloset)

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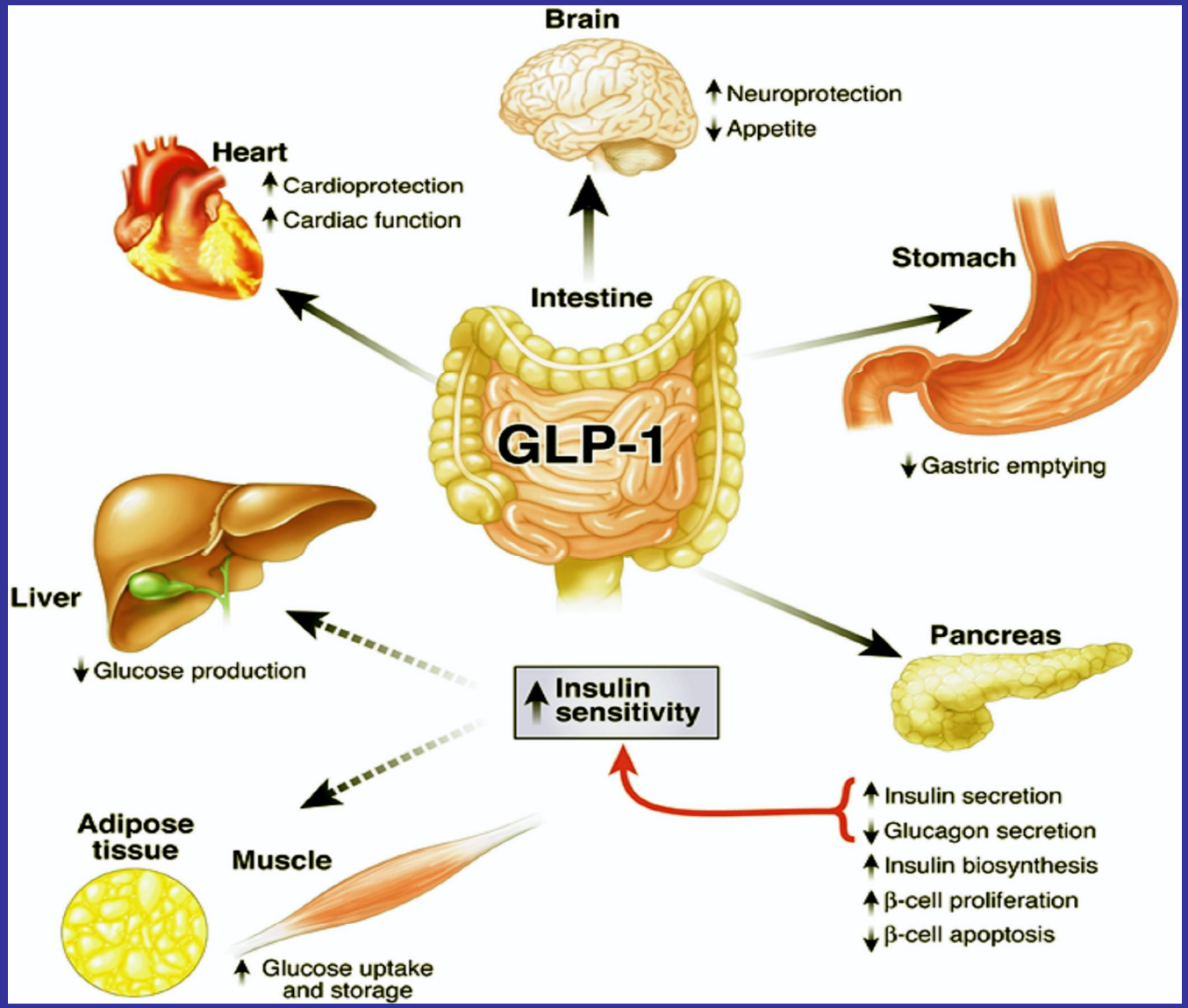
Incretin-Based Therapies

- GLP-1 receptor agonists
  - *GLP-1 mimetics*
    - Exenatide
    - Exenatide once weekly (under FDA review)
  - *GLP-1 analogs*
    - Liraglutide
    - Numerous investigational agents
- Incretin enhancers (DPP-4 inhibitors)
  - *Sitagliptin*
  - *Saxagliptin*
  - *Numerous investigational agents*

The Diverse Actions of GLP-1

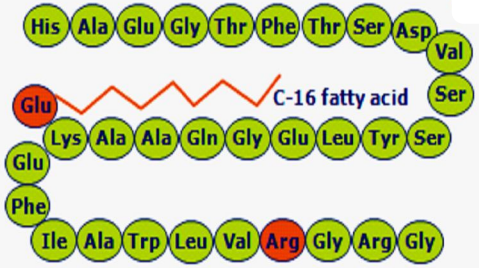


Baggio LL, et al. *Gastroenterology*. 2007;132:2131-2157.

Native human GLP-1

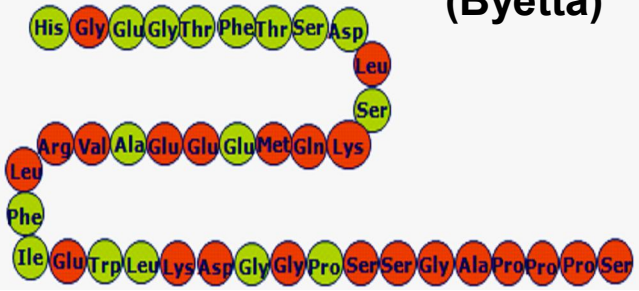
Liraglutide (Victoza)

97% amino acid homology to human GLP-1



Exenatide (Byetta)

53% amino acid homology to human GLP-1



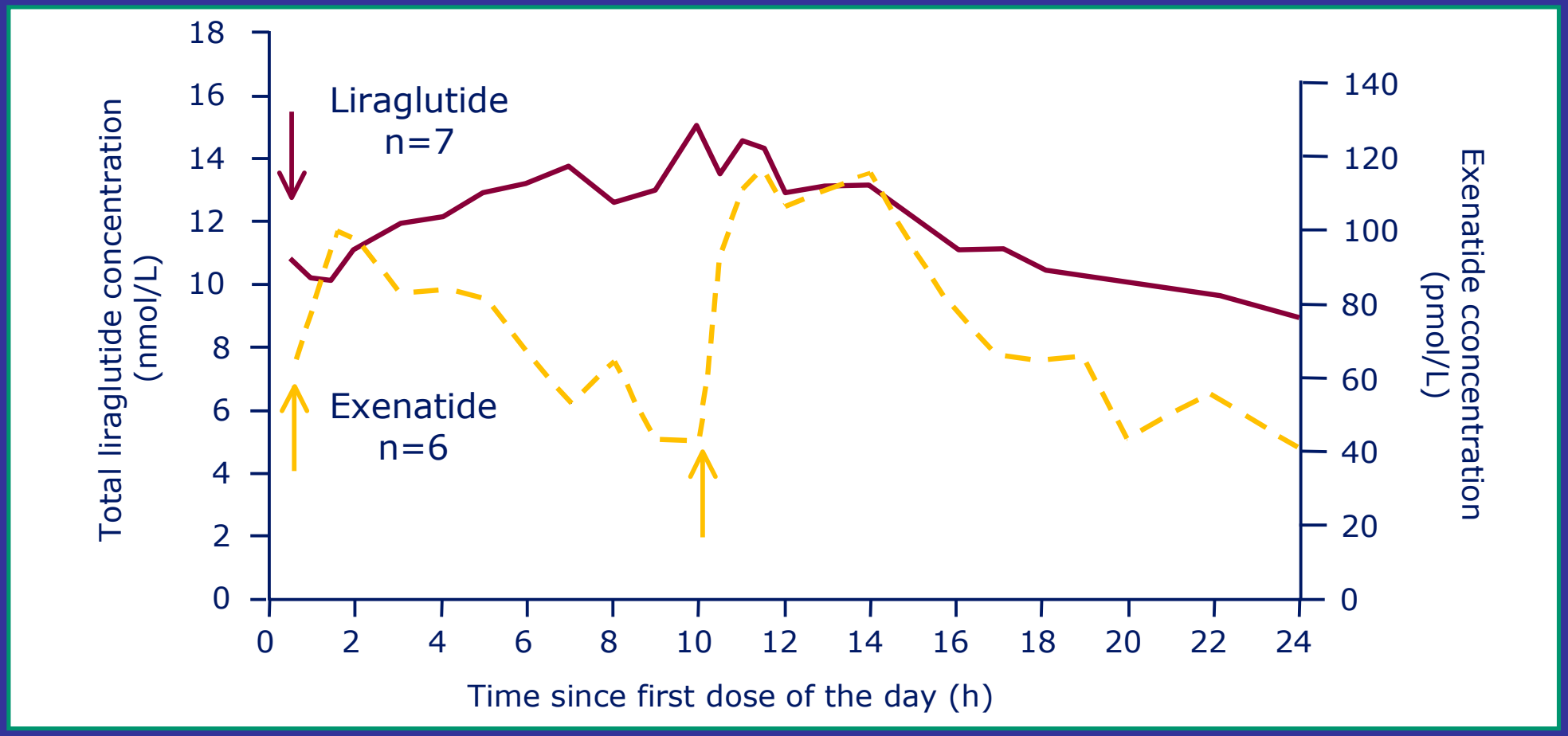
Differences between liraglutide and exenatide

	Liraglutide[1]	Exenatide[2]
Dosing guidelines	Once daily, independent of meals	Twice daily, within 60 min before morning and evening meals
Half-life	13 h	2.4 h
Maximum dose	1.8 mg	10 mcg (BID)
Renal elimination	No	Yes
Homology to native GLP-1	97%	53%
Antibodies	8.6%	44%

BID, twice daily

[1]Victoza PI, 2010; [2]Byetta PI, 2009.

Steady state levels of liraglutide and exenatide

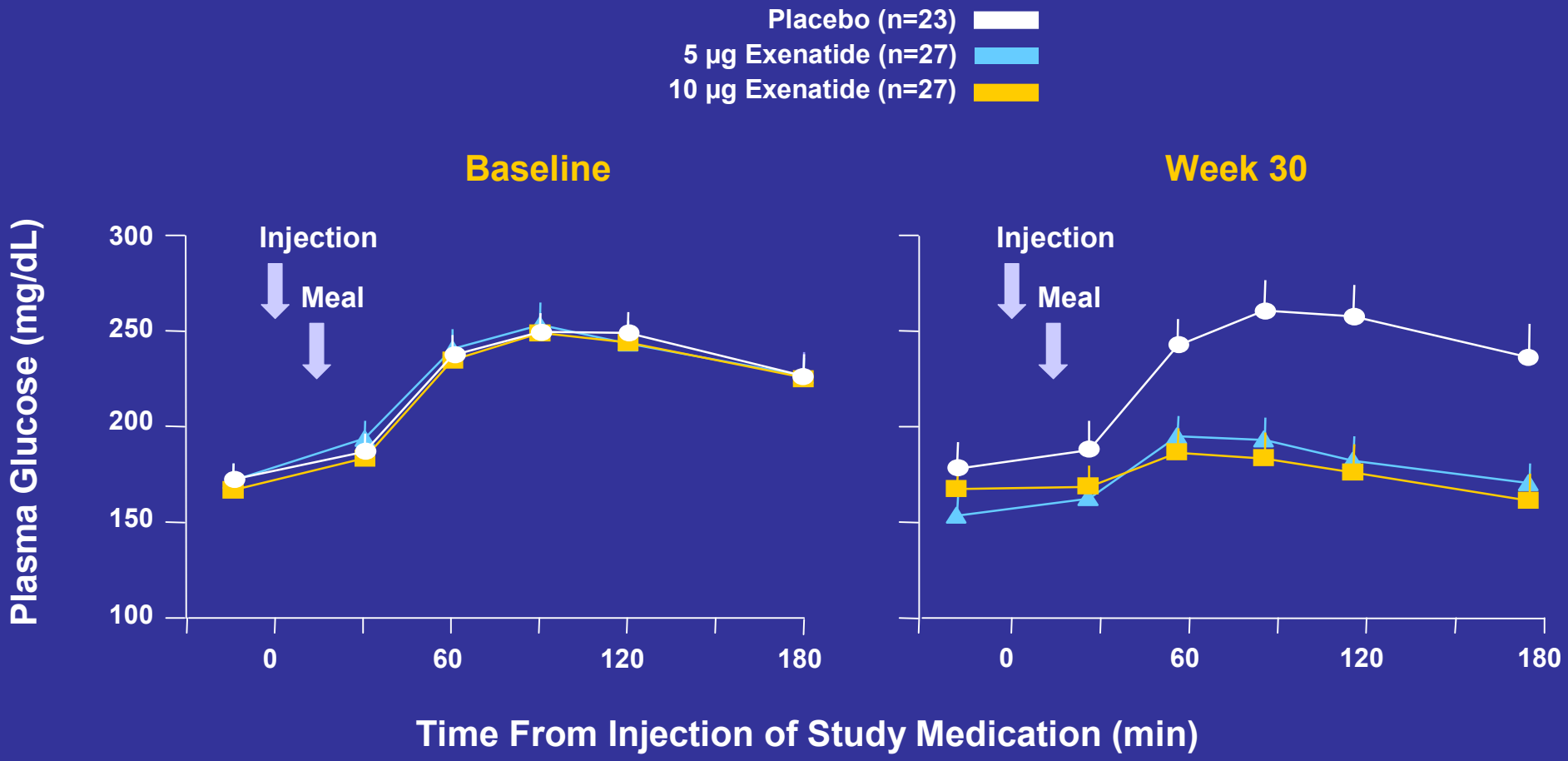


Exenatide was injected in the morning (timepoint 0 h) and the evening (timepoint 10 h); depicted by arrows

Rosenstock *et al*. *Diabetes* 2009;58(Suppl 1):558-P

Exenatide: Post Meal Glucose

Exenatide – Metformin – Sulfonylurea Combination



Kendall DM, Riddle MC, Rosenstock J et al. *Diabetes Care* 2005.

Placebo vs 5-µg and 10-µg exenatide :
$P \leq 0.001$ for AUC glucose

Exenatide: Change in A1c and Weight (vs Placebo)

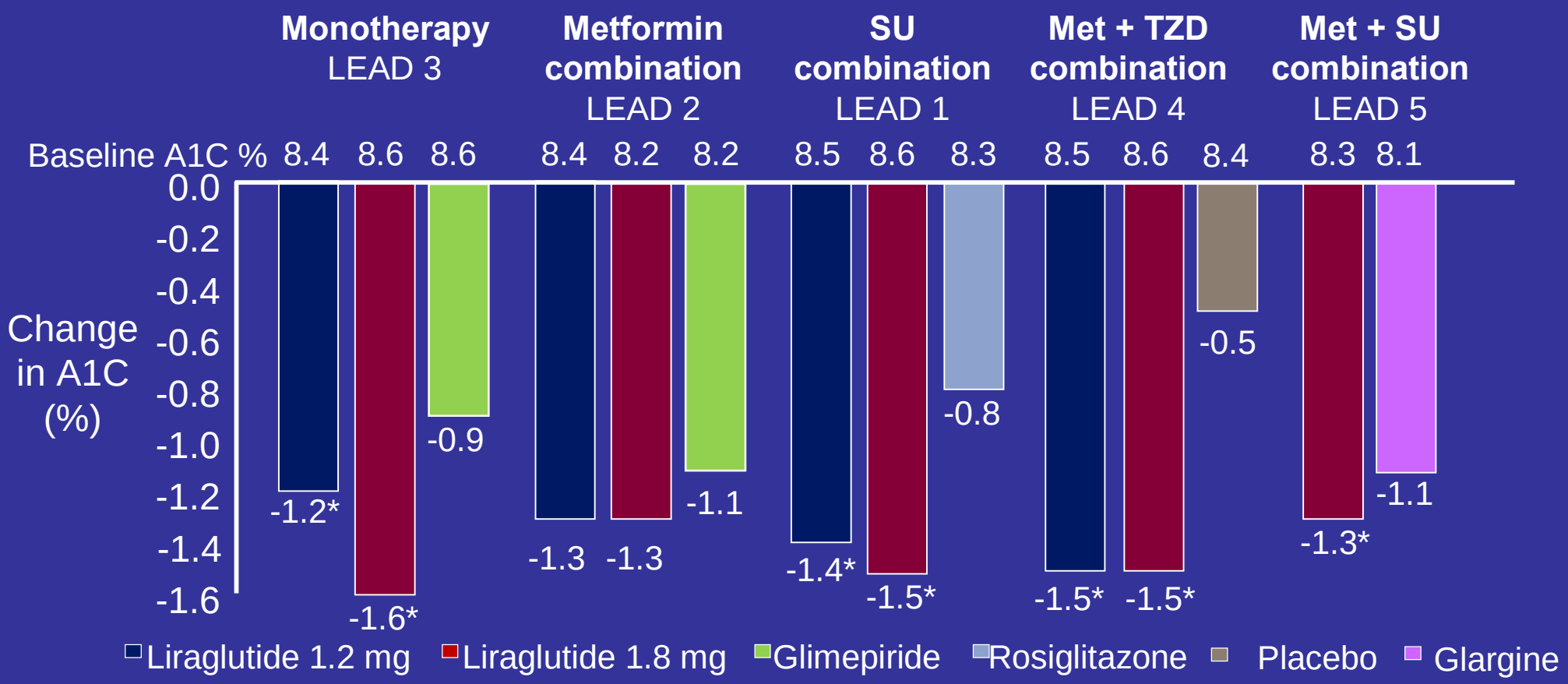
Add on to:	Duration	Exenatide 10 μg bid	
		A1C Change in % (baseline)	Weight change in kg (baseline)
Monotherapy	24 weeks	-0.7 (7.8)	-1.5 (86.2)
Metformin	30 weeks	-0.9 (8.2)	-2.4 (100.9)
Sulfonylurea	30 weeks	-1.0 (8.6)	-0.9 (95.2)
Metformin + sulfonylurea	30 weeks	-1.0 (8.5)	-0.7 (98.4)
Glitazone ± metformin	16 weeks	-0.9 (7.9)	-1.5 (97.5)

Exenatide prescribing information. Amylin Pharmaceuticals Inc; 2009.

Exenatide: Adverse Events

- Almost 50% of patients will have one or more episodes of nausea or other GI adverse event
  - *Generally early in the course; less frequent with time*
  - *~5% will stop therapy due to nausea or vomiting*
  - *Minimized by starting with a low dose bid for 4 weeks, then titrate as tolerated to 10 μg bid*
  - *Also minimized by administering exenatide just before meals until well tolerated; subsequently taking exenatide 30-60 minutes before meals may be associated with greater weight loss*
- Sulfonylurea-related hypoglycemia can be increased
  - *Generally reduce sulfonylurea dose when initiating therapy with exenatide*
- Antibodies of unclear significance
- Pancreatitis – rare; an association but no proven causation
- Renal failure – rare; related to dehydration in the setting of nausea and vomiting

Liraglutide: A1C



Significant *vs. comparator; #Change in HbA_{1c} from baseline for overall population (LEAD 4,5) add-on to diet and exercise failure (LEAD 3); or add-on to previous OAD monotherapy (LEAD 2,1).

Buse JB, et al. *Lancet*. 2009;374:39-47. Garber A, et al. *Lancet*. 2009;373:473-439. Marre M. *Diabet Med*. 2009;26:268-278. Nauck M. *Diabetes Care*. 2009;32:84-90. Russell-Jones D, et al. *Diabetologia*. 2009;52:2046-2055. Zinman B, et al. *Diabetes Care*. 2009;32:1224-1230.

Definition of two composite endpoints

Composite 1:

- HbA_{1c}<7.0% +
- no weight gain +
- no confirmed hypoglycaemia (minor or severe)

Of clinical and patient interest

Composite 2:

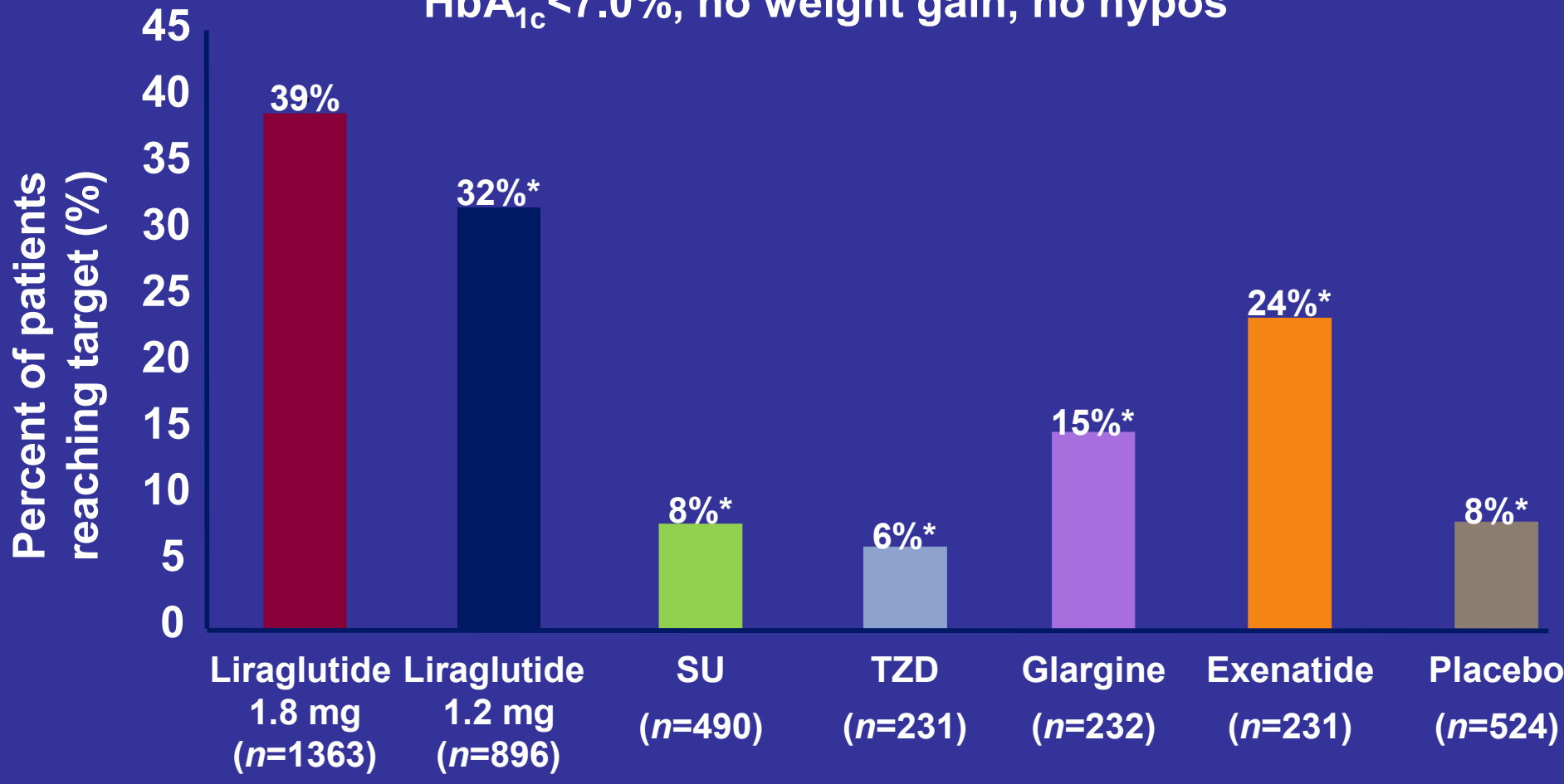
- HbA_{1c}<7.0% +
- no weight gain +
- SBP<130 mmHg

Includes 3 goals set by ADA 2008 Standards of Care

Zinman B, Buse J, et al. *Diabetes 2009; 58 (suppl. 1): 537-P.*

Composite endpoint 1

HbA_{1c}<7.0%, no weight gain, no hypos

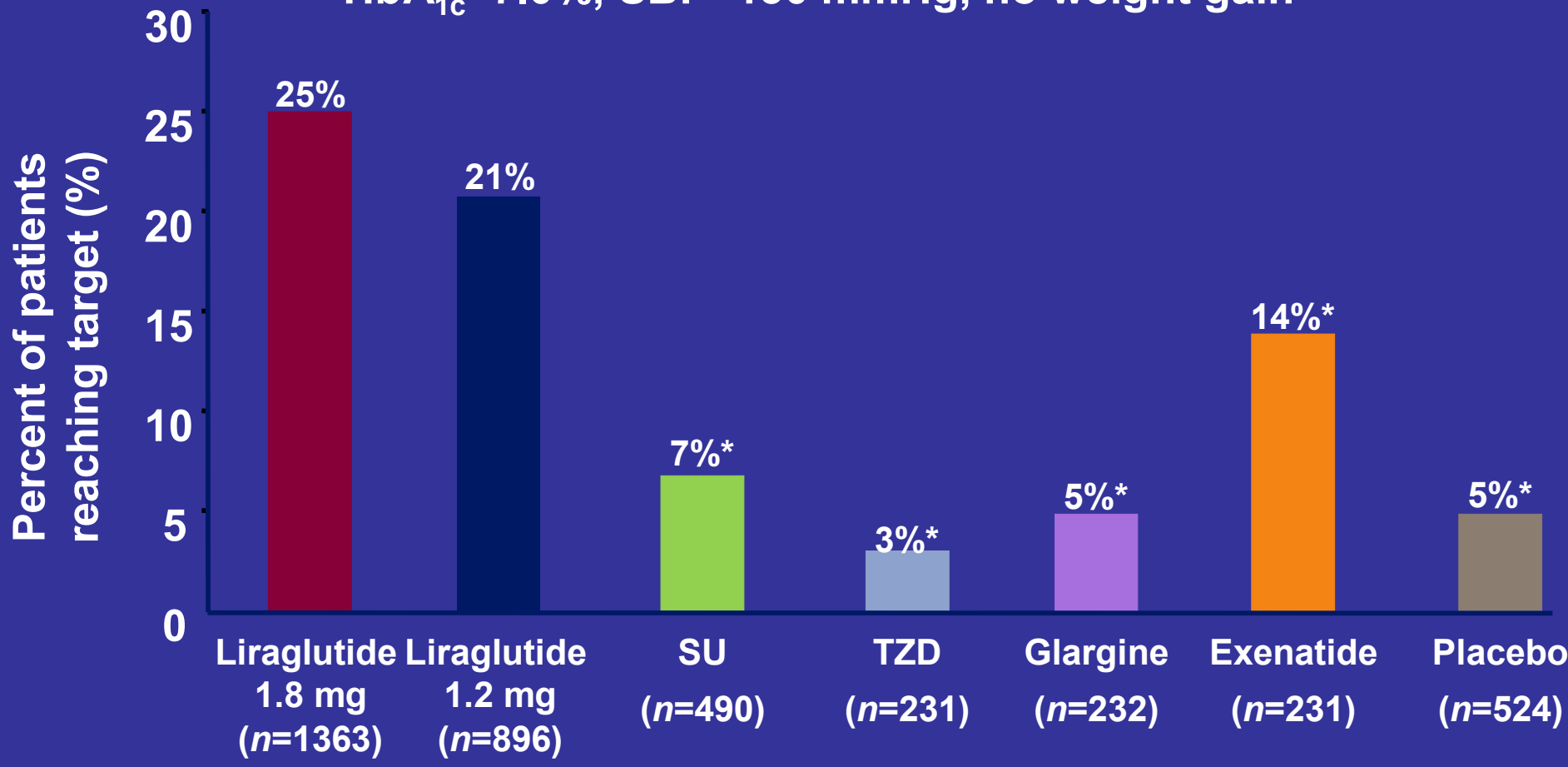


*p<0.01 vs. liraglutide 1.8 mg

Zinman B, Buse J, et al. *Diabetes 2009; 58 (suppl. 1): 537-P.*

Composite endpoint 2

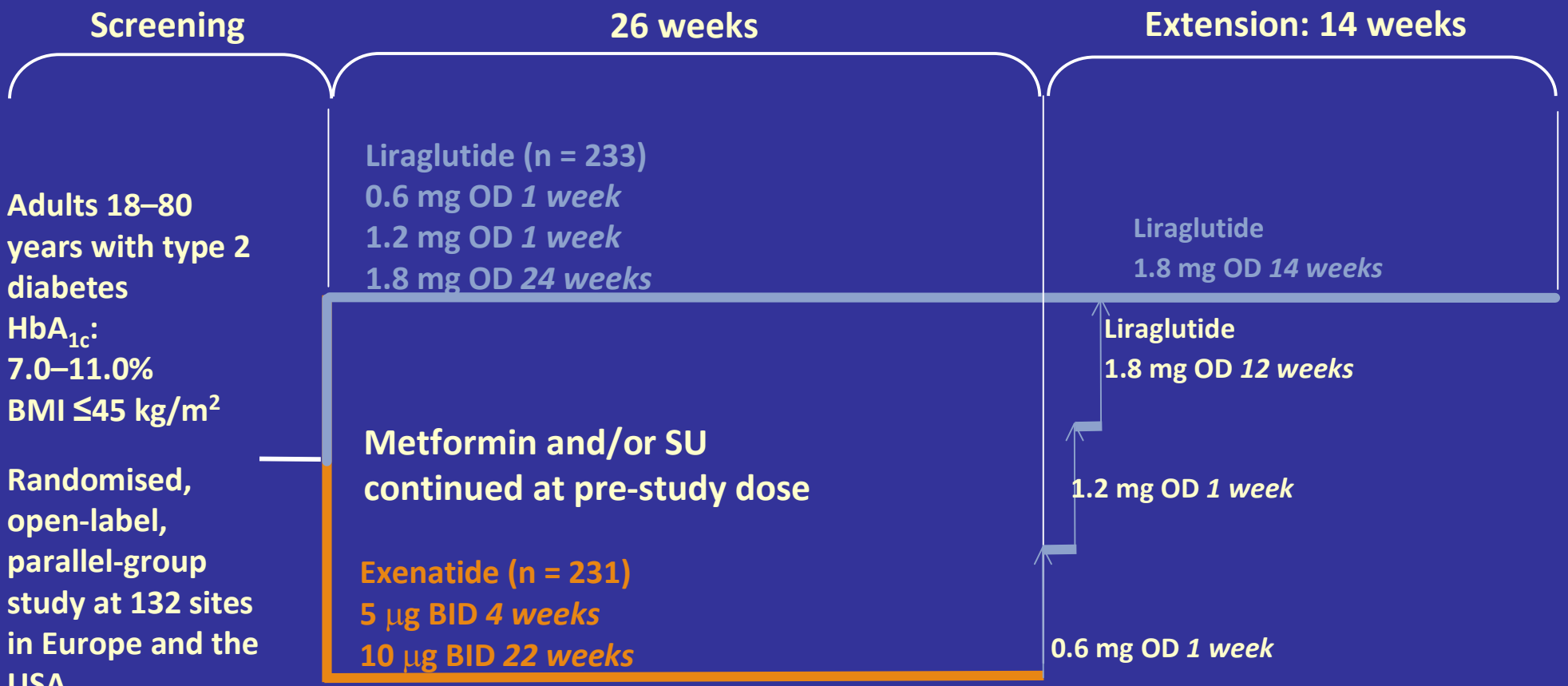
HbA_{1c}<7.0%, SBP<130 mmHg, no weight gain



*p<0.01 vs. liraglutide 1.8 mg

Zinman B, Buse J, et al. *Diabetes 2009; 58 (suppl. 1): 537-P.*

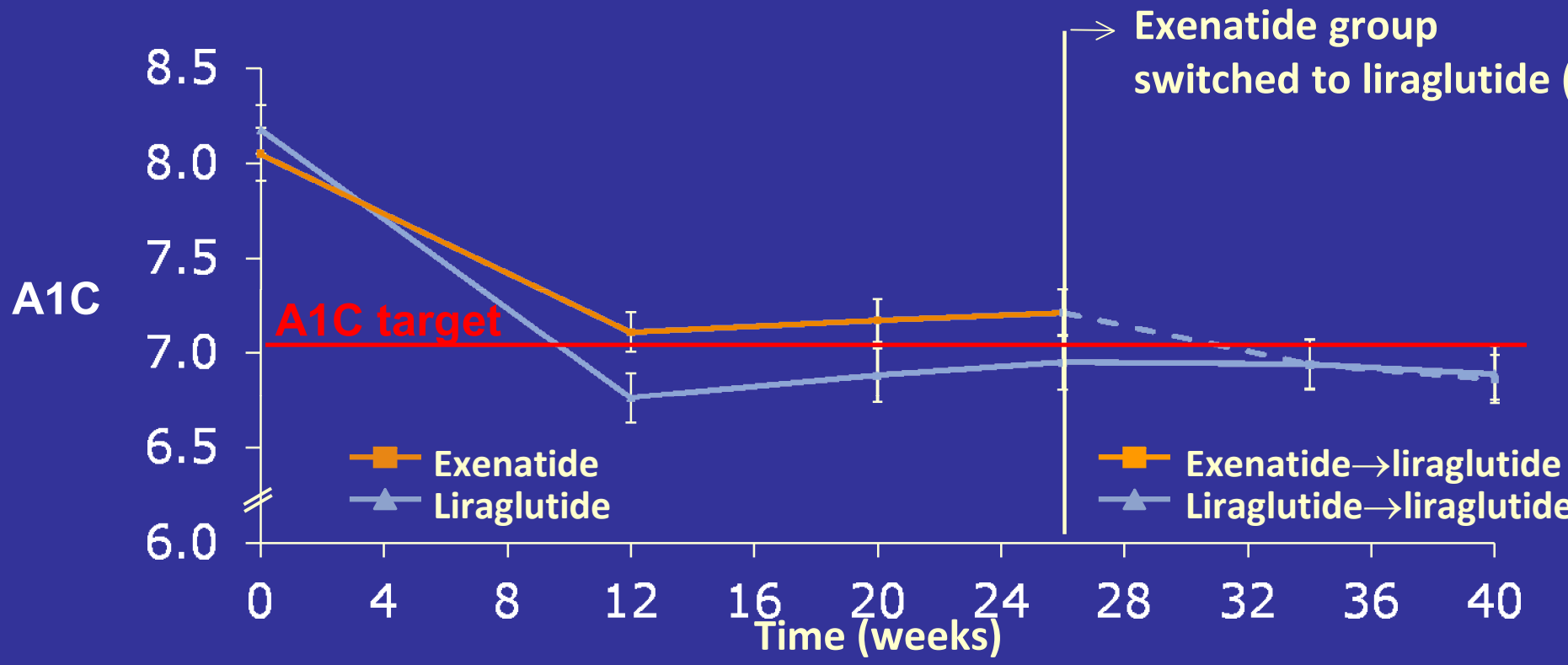
Design of LEAD-6 study



OD, once daily; BMI, body mass index

Buse *et al. Lancet* 2009;374(9683):39-47; Buse *et al. Diabetes* 2009;58 (Suppl 1):A159

LEAD-6: A1C



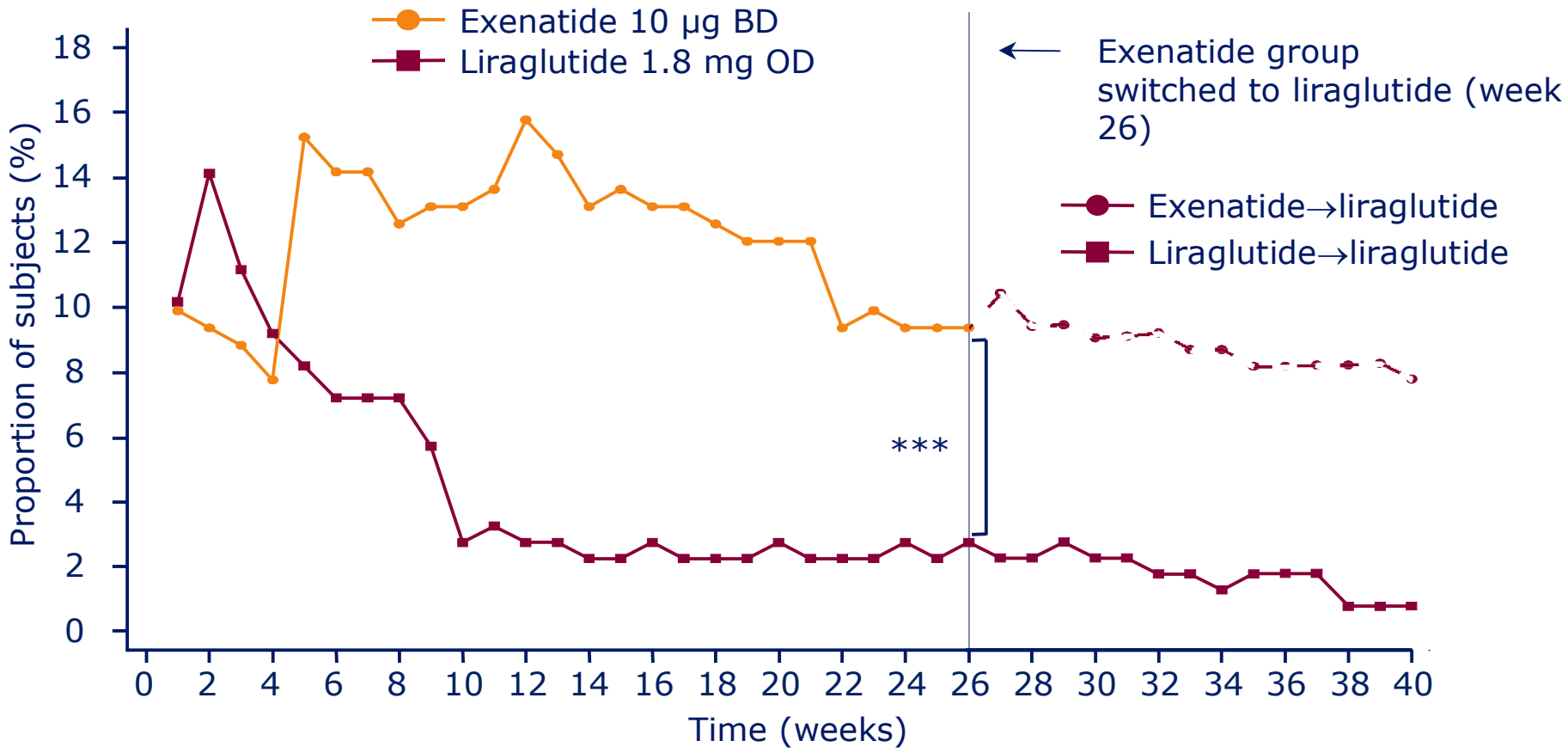
Mean (2 SE)

Data from weeks 0–26 are only for patients who participated in the LEAD-6 extension phase

Buse *et al. Diabetes* 2009;58 (Suppl 1):A159

LEAD-6: Nausea

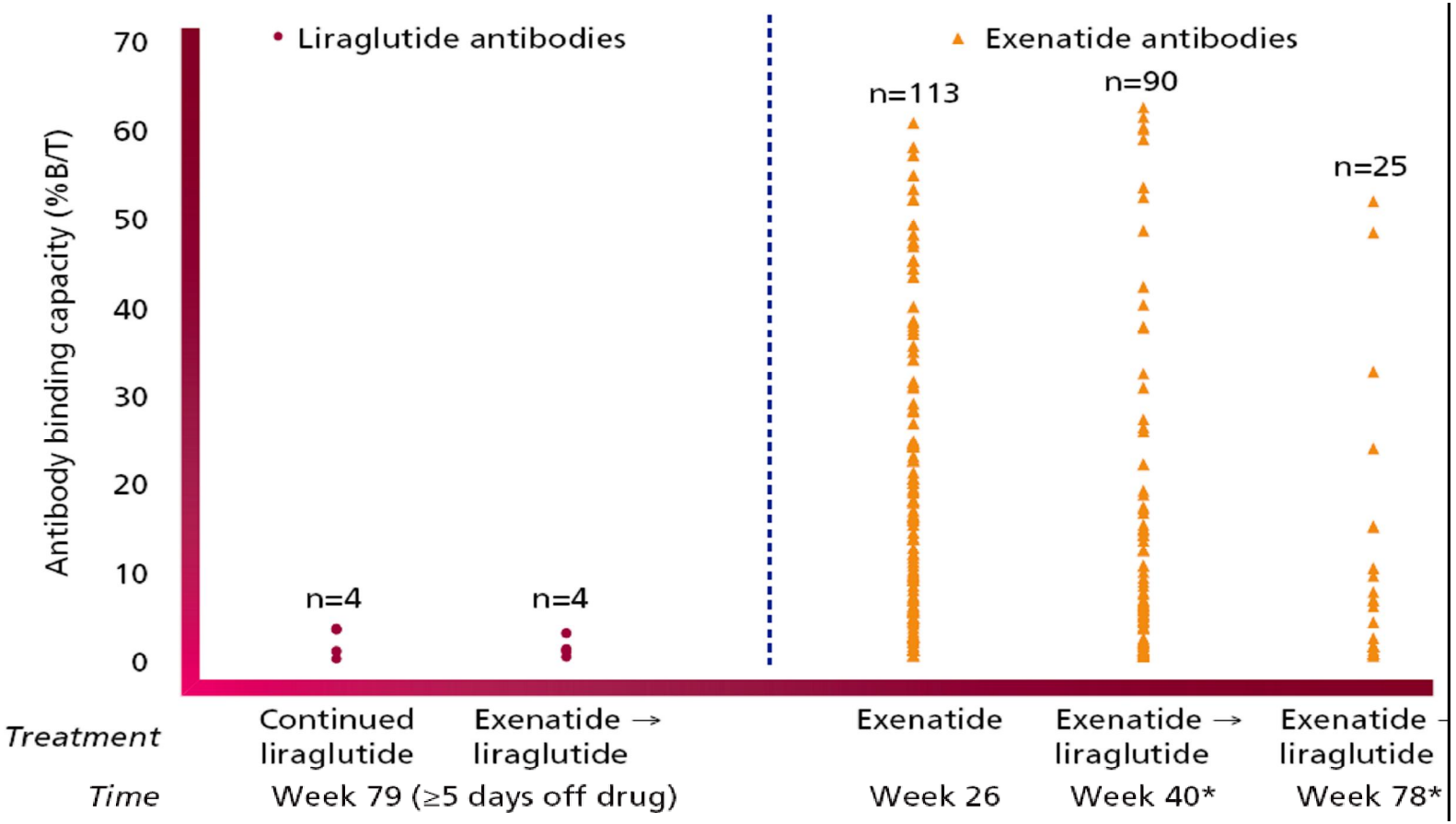
Data from weeks 0–26 are only for patients who participated in the LEAD-6 extension phase



Data are number (%) of patients exposed to treatment (safety population); estimated treatment difference in changes for full population at week 26 ***$p<0.0001$ (estimated treatment rate ratio for liraglutide vs. exenatide, 0.448)

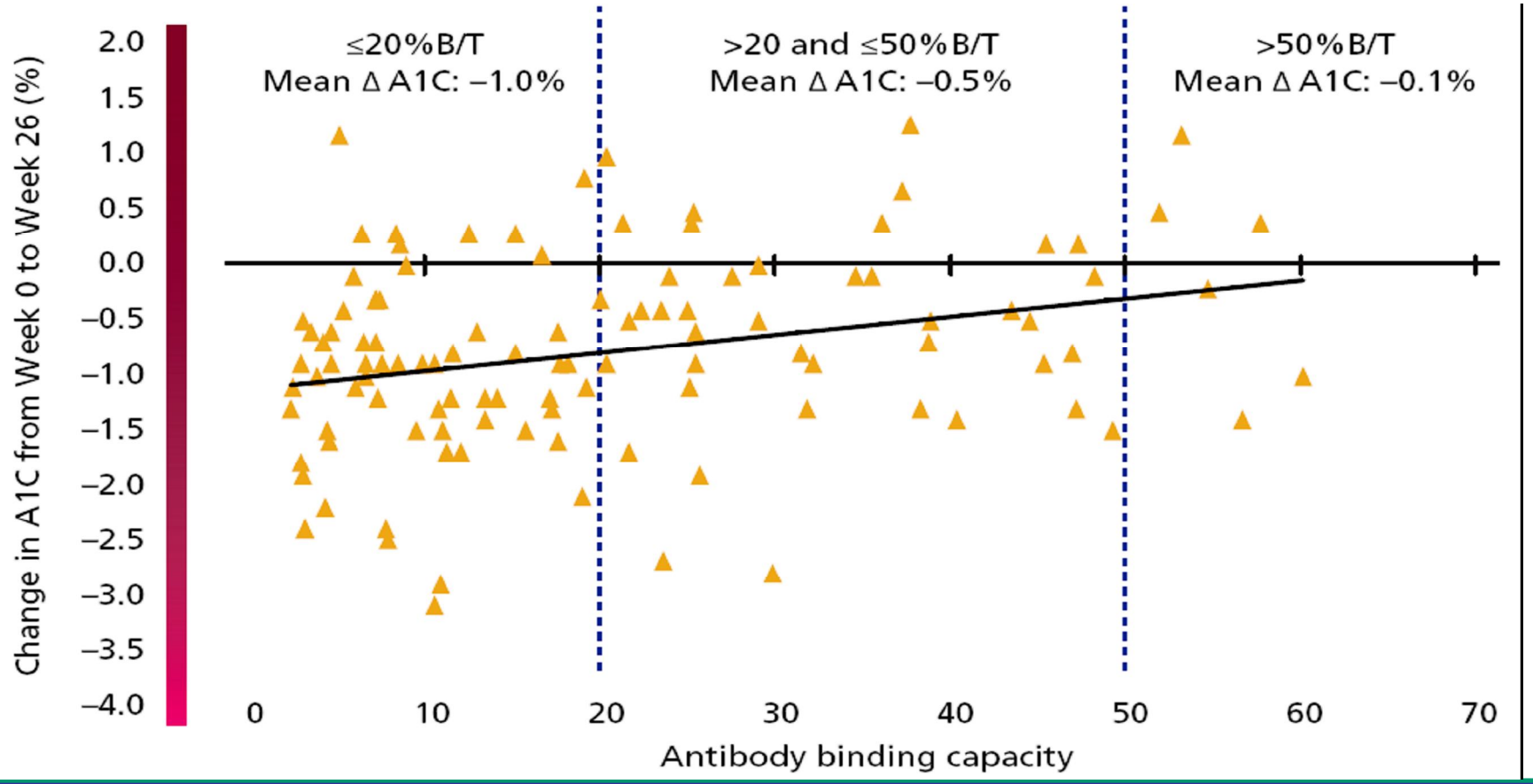
Buse *et al. Lancet* 2009;374(9683):39–47 (LEAD-6); Buse *et al. Diabetes Care* 2010; Available online (LEAD-6 Ext)

LEAD-6: Antibody



LEAD-6: Antibody

Correlation between exenatide antibody titer levels and change in A1c



Change in A1C after switching from exenatide to liraglutide	**≤20% B/T (n=66)** **Week 26 A1C: 7.1%** **-0.25%**	**>20% B/T (n=17)** **Week 26 A1C: 8.1%** **-0.85%**

Buse et al, ADA 676-P 2010

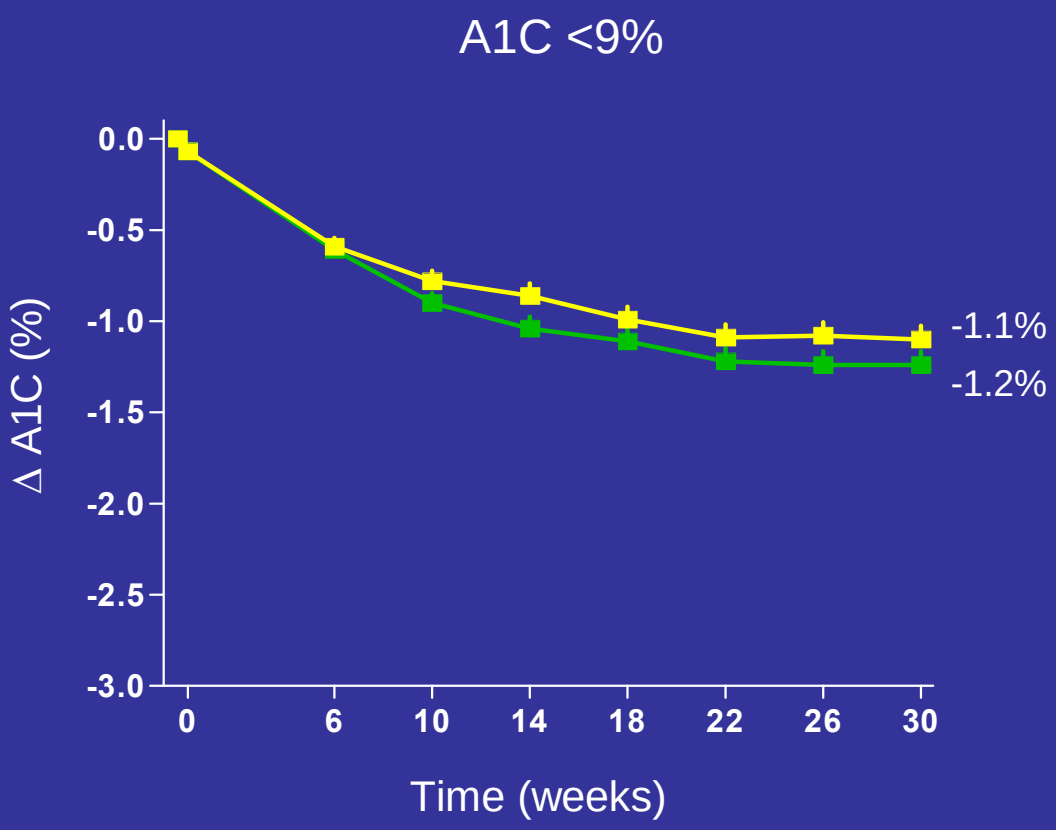
Liraglutide QD vs. Exenatide BID: Other Effects

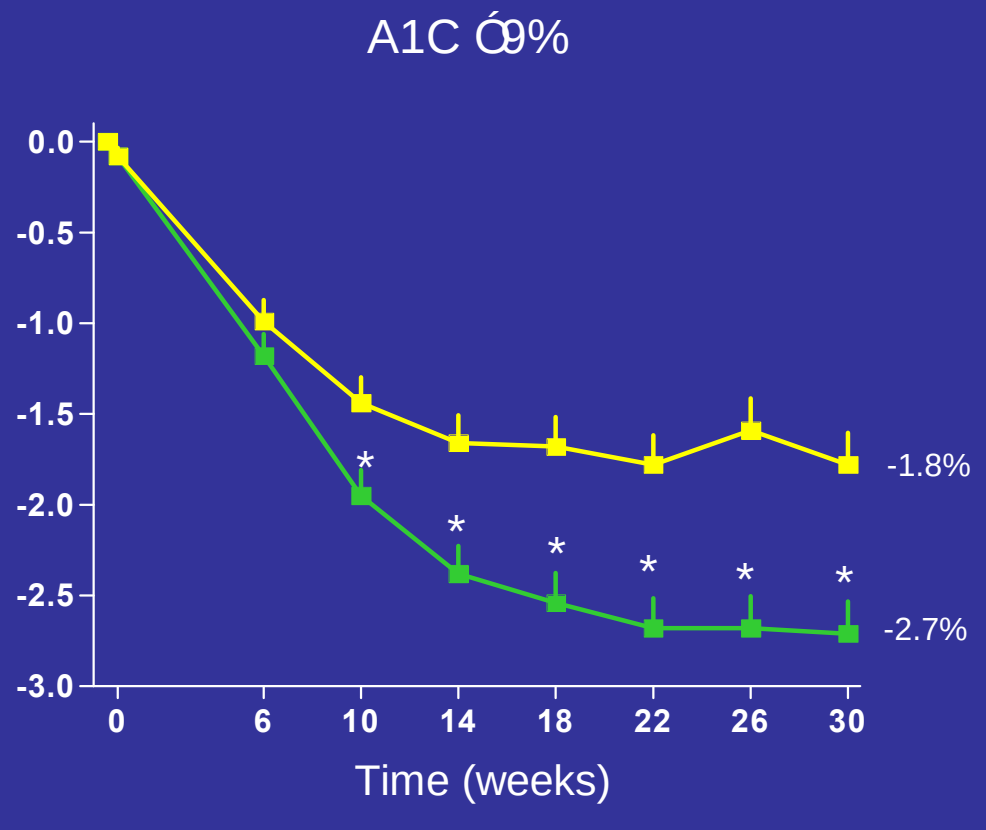
- **Liraglutide produced greater effects on:**
  - **Fasting plasma glucose**
  - **Triglycerides**
  - **Beta-cell function – HOMA-B**
- **Liraglutide produced lesser effects on:**
  - **Hypoglycemia**
  - **Persistent nausea**

Blonde L, et al. *Can J Diabetes.* 2008;32(suppl):A107. (LEAD-6).

Exenatide Once-Weekly vs. Exenatide BID: A1C

overall populations EOW -1.9%, BID -1.5%, p<0.01 (baseline 8.3%)





Data are LS mean (SE); *p<0.05, QW vs BID

Drucker DJ, Buse JB, et al. *Lancet.* 2008;372:1240-1250.

Long-Acting GLP-1 Agonists: Adverse Events

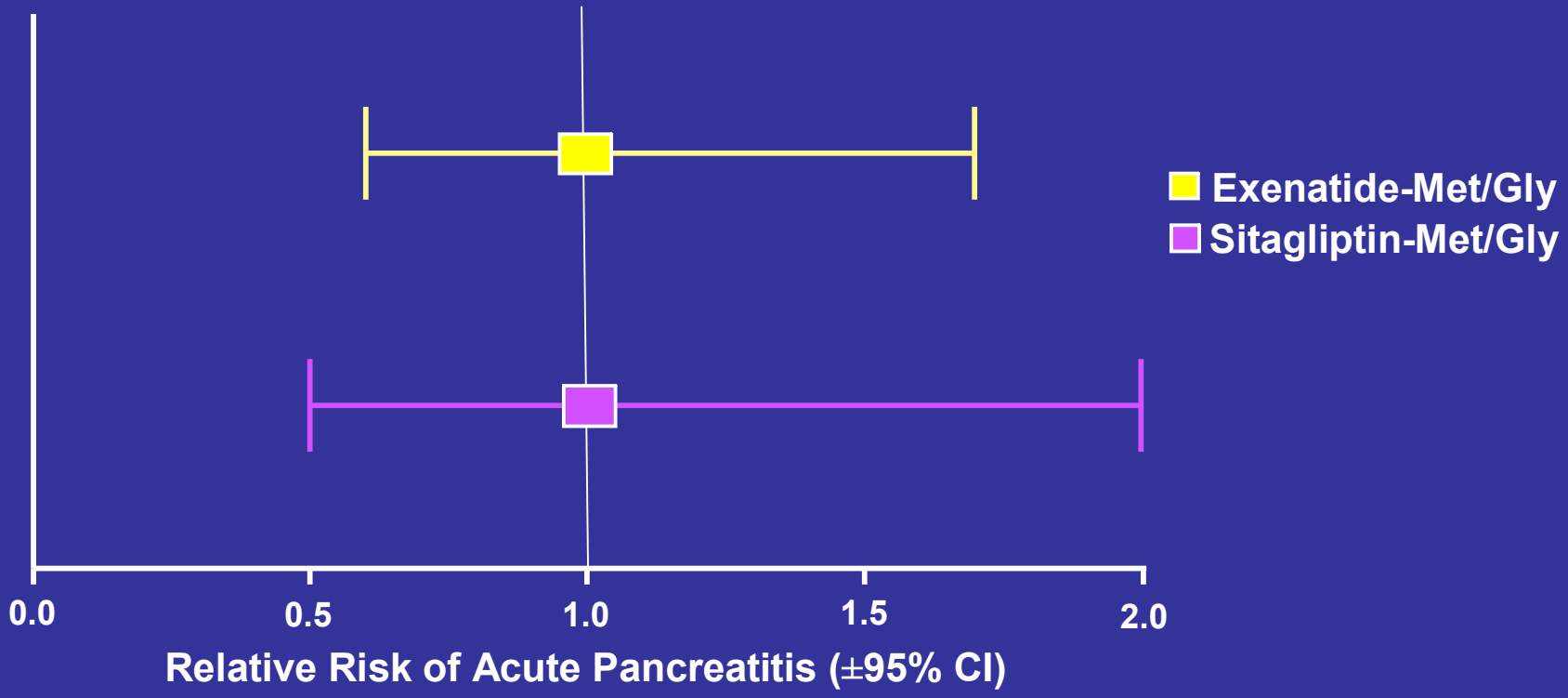
- Generally fewer GI adverse events than exenatide twice daily
- Sulfonylurea-related hypoglycemia can be increased
- Antibodies
  - *Minimal with liraglutide*
- Pancreatitis – rare; an association but no proven causation
- Renal failure – rare; related to dehydration in the setting of nausea and vomiting
- Skin reactions
- Medullary carcinoma of the thyroid in rodents

Exenatide, DPP-4 Inhibitors and Long-Acting GLP-1 Agonists: Similarities and Differences

Properties/Effect	Exenatide[1]	DPP-4 Inhibitor[1]	Liraglutide, Exenatide-OW[2,3]
Glucose-dependent ↑ insulin secretion	Yes	Yes	Yes
Glucose-dependent ↓ glucagon	Yes	Yes	Yes
Slows gastric emptying	Yes	No	Little or no
Effect on body weight	Weight loss	Weight neutral	Weight loss
Effect on A1c	~1%	<1%	>1%
Effect on fasting glucose	Modest	Modest	Good
Effect on postprandial glucose	Good	Modest	Modest
Effect on CVD risk factors	Improve (with weight loss)	No consistent change	Improve
Side effects	Nausea (?pancre-atitis, CRF)	~ None observed (pancreatitis)	Less nausea, skin, (?pancreatitis, ?CRF, ?MTC)
Administration	Subcutaneous Twice daily	Oral Once daily	Subcutaneous Daily or weekly

1. Amori RE, et al. *JAMA*. 2007;298:194-206.
2. Exenatide LAR (once weekly): Drucker DJ, et al. *Lancet*. 2008;372:1240-1250.
3. Liraglutide: Buse JB, et al. *Lancet*. 2009;374:39-47.

Absolute and Relative Risk of Acute Pancreatitis With Anti-diabetic Agents in Human Subjects



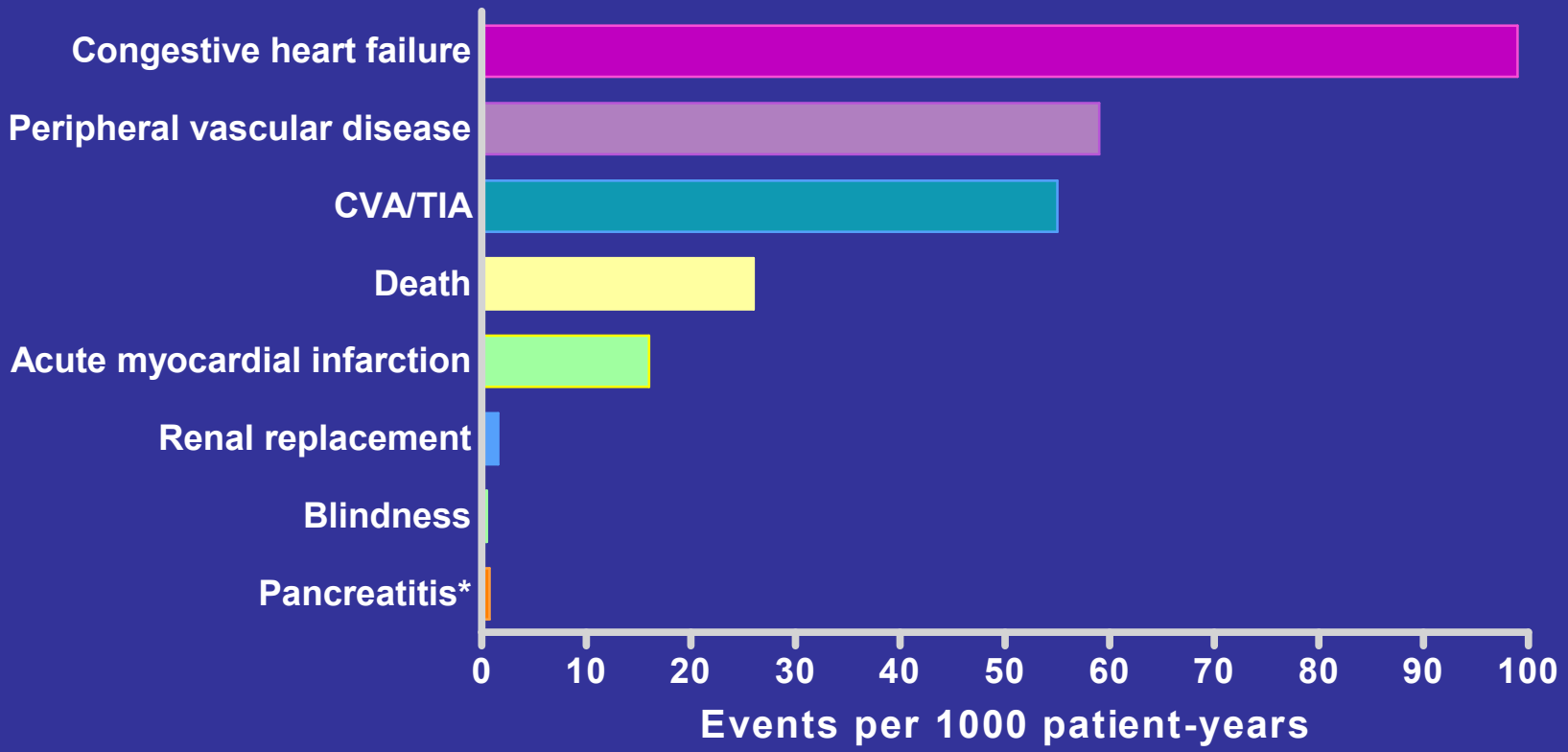
Å The absolute risk of acute pancreatitis was comparable among initiators of exenatide and sitagliptin

Drug Pair 1: Exenatide 0.13% (N = 27,996); Met/Gly 0.13% (N = 27,983)
Drug Pair 2: Sitagliptin 0.12% (N = 16,267); Met/Gly 0.12% (N = 16,281)

Dore D, et al. Current Medical Research and Opinion. 2009; 25(4):1019-1027.

Pancreatitis: Risk in Type 2 Diabetes

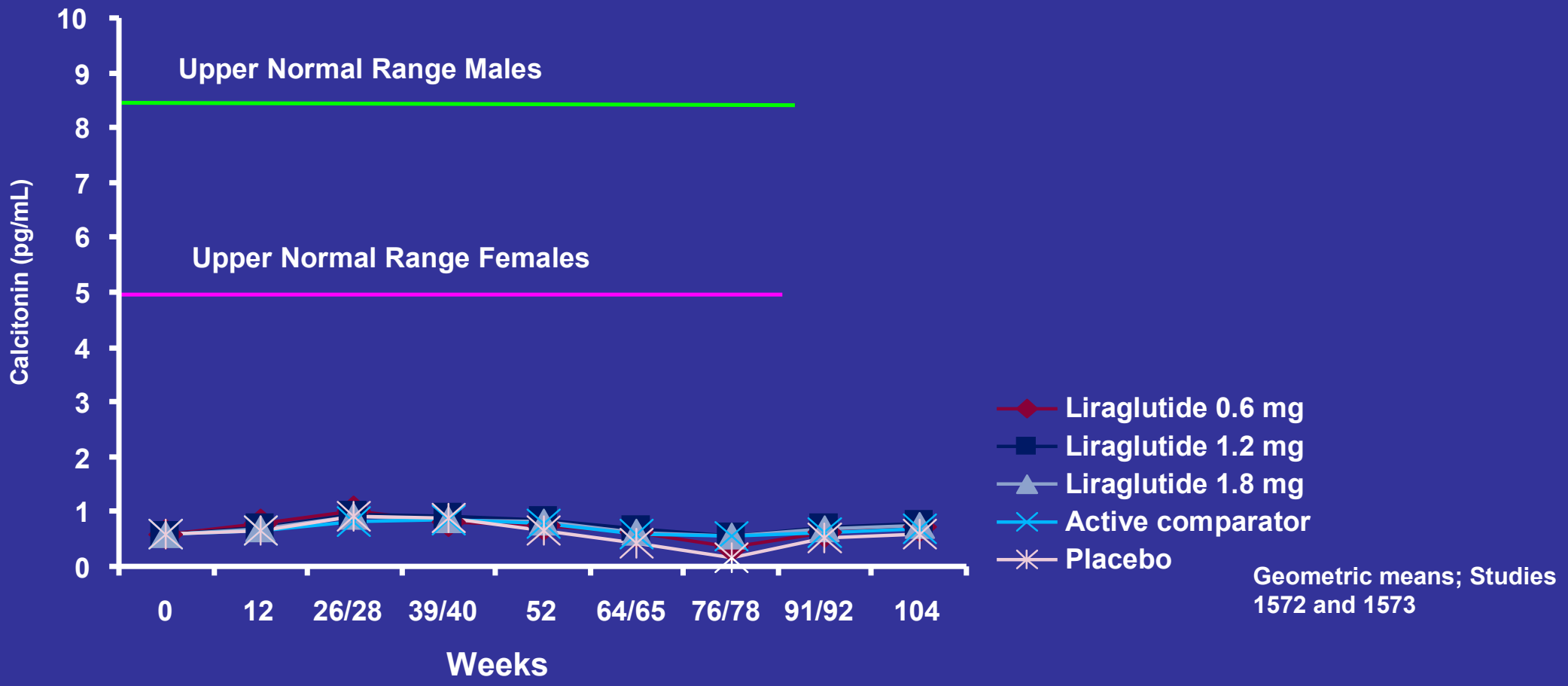
Adjusted event rates with diabetes relative to without diabetes



*Rate estimated from insurance claims database study
CVA/TIA, cerebrovascular accident/transient ischemic attack.
Foley RL, et al. *J Am Soc Nephrol* 2005;16:489-495. Trautner C et al. *Diabetes Care* 1997;20:1147-53.
Frey CF, et al. *Pancreas* 2006;33:336-344. Noel R, et al. *Diabetes Care* 2009; 32:834-838

Calcitonin Levels Observed in LEAD Studies of Liraglutide in Human Diabetic Subjects

- Compared to variations during study (see placebo curve), differences between comparators are extremely small and far within normal ranges



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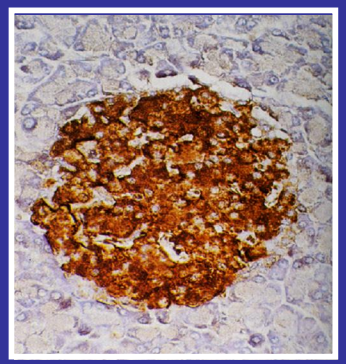
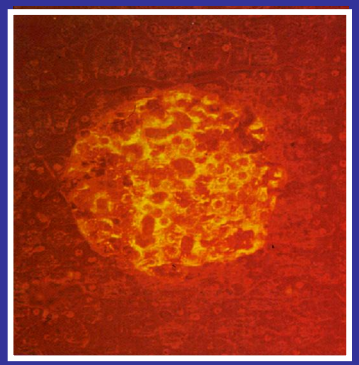
Amylin: The Second β-Cell Hormone

- First reported in 1987
- Colocated and cosecreted with insulin from pancreatic β cells
- Not synonymous with "amyloid deposits"



Amylin

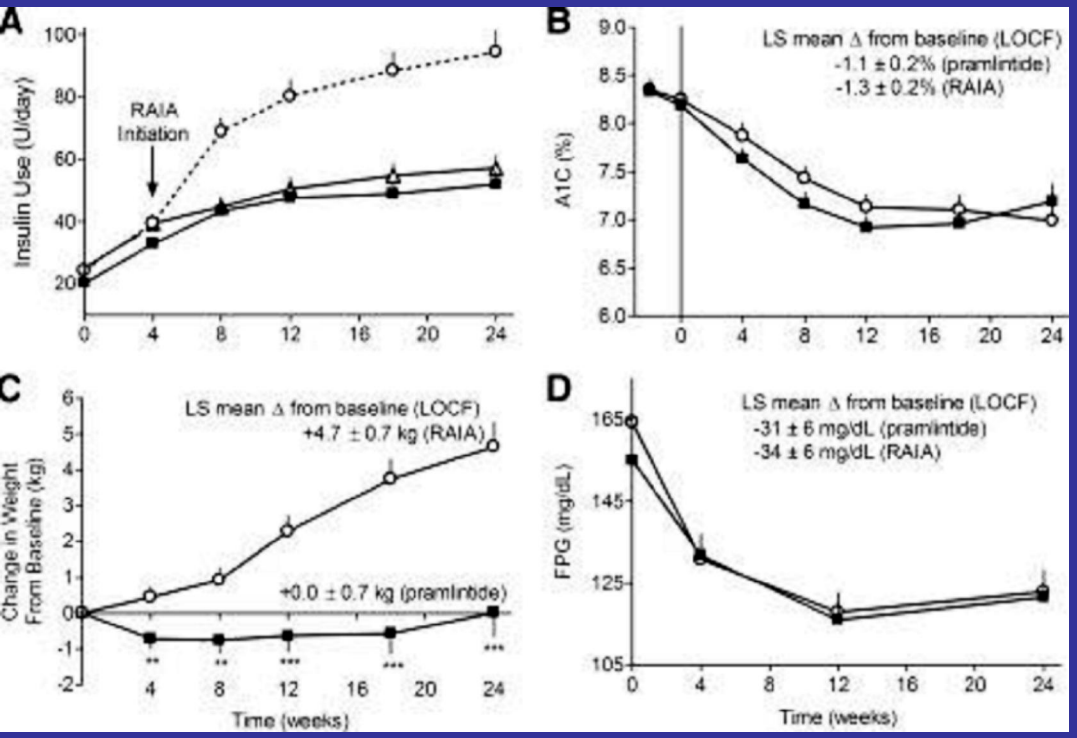


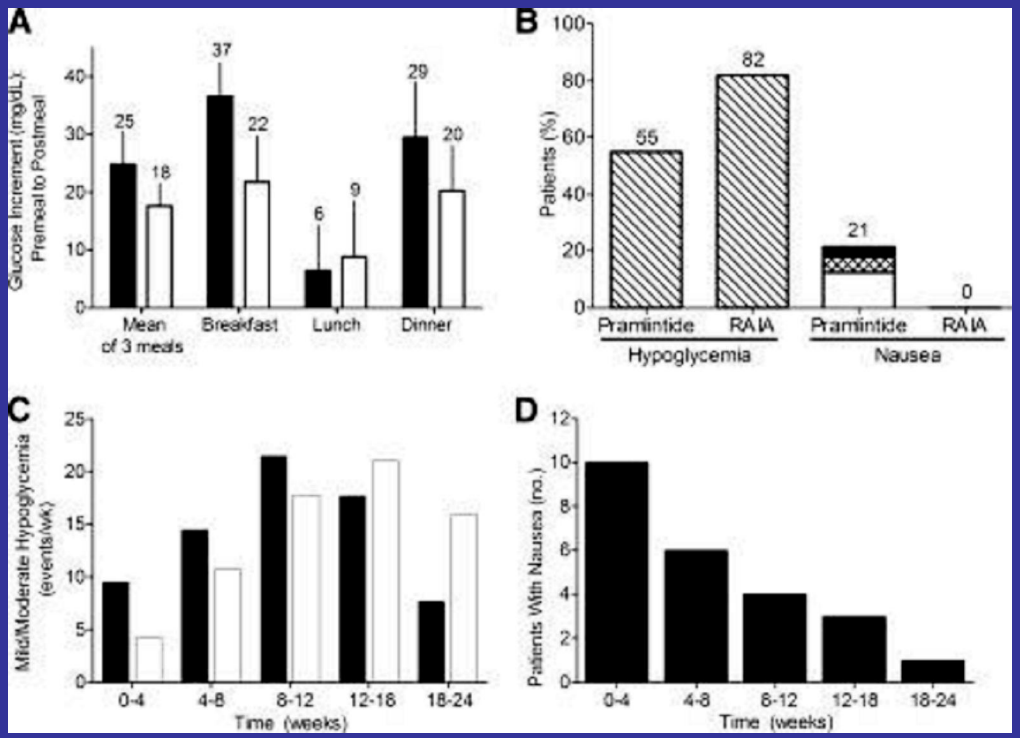
Insulin

Unger RH, Foster DW: Diabetes mellitus. In *Williams Textbook of Endocrinology,* Wilson JD, Foster DW, Eds. Philadelphia, Pa., WB Saunders Company, 1992, p. 1273–1275

Pramlintide (Symlin)

113 patients were randomly assigned 1:1 to addition of mealtime pramlintide (120 mcg) or a titrated rapid-acting insulin analog to basal insulin and prior oral antihyperglycemic drugs. The basal insulin dosage was titrated from day 1, seeking fasting plasma glucose 70-100 mg/dl. Pramlintide and an RAIA were initiated on day 1 and week 4, respectively.





Riddle M, et al. Diabetes Care. 2009 Sep;32(9):1577-82

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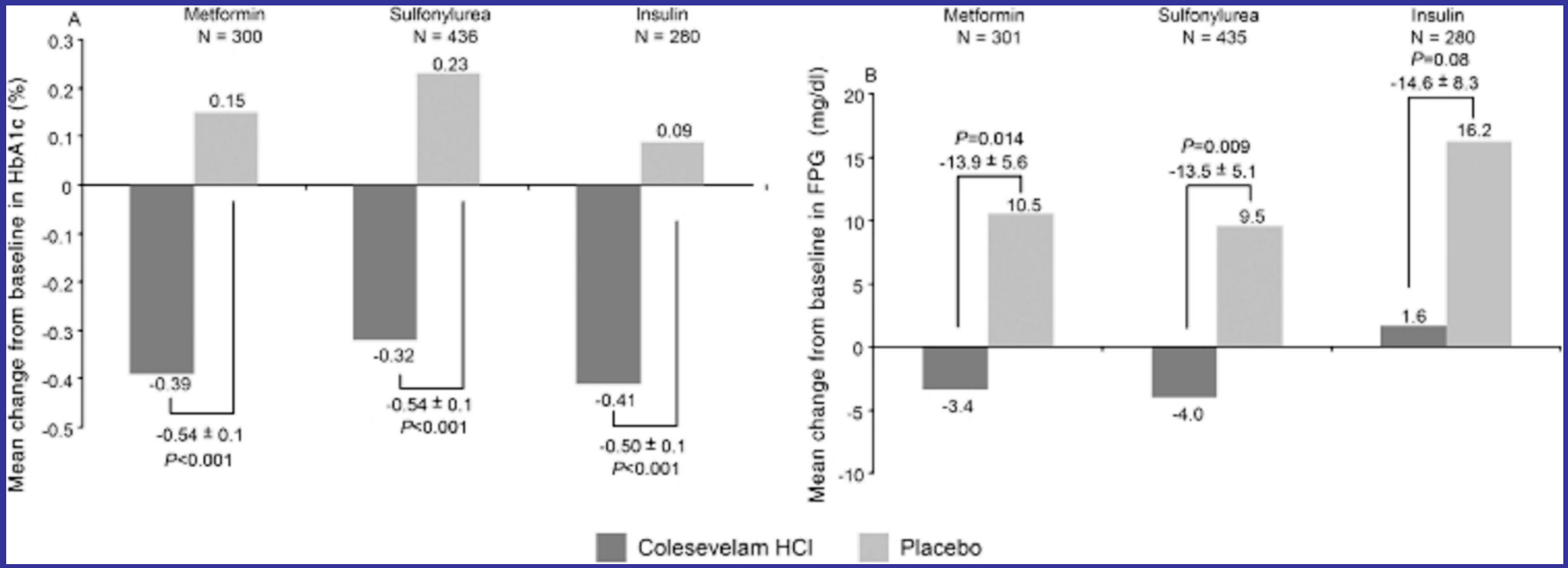
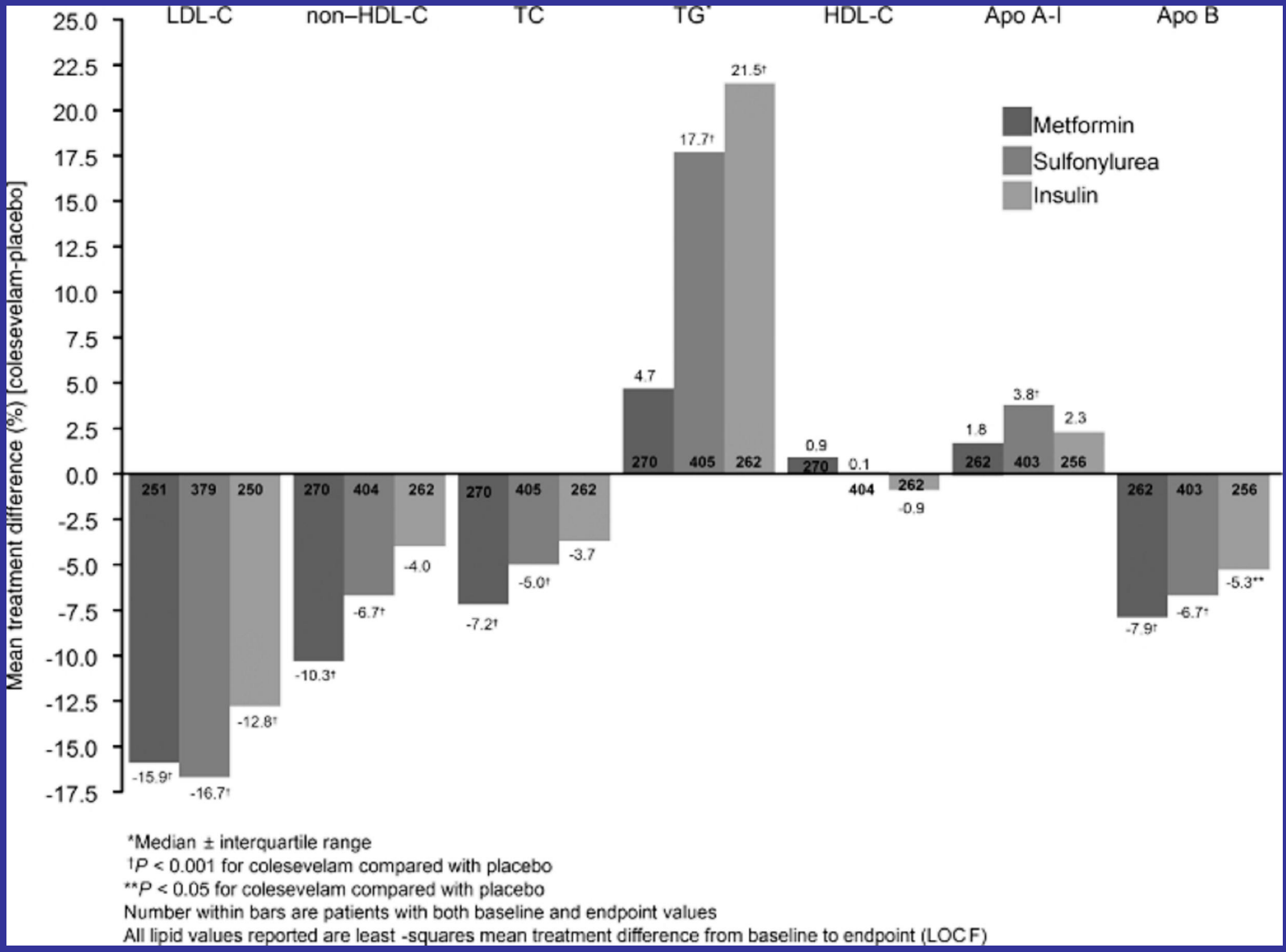
Colesevelam



Fonseca V, et al. Diabetes Obes Metab. 2010 May; 12(5): 384ï 392.

Colesevelam



Fonseca V, et al. Diabetes Obes Metab. 2010 May; 12(5): 384ï 392.

Colesevelam

MECHANISMS:

The mechanism(s) by which colesevelam lowers glucose levels in patients with T2DM is not yet clearly understood. However, there is increasing evidence that the glycaemic effects of bile acid sequestrants may occur through farnesoid X receptor (FXR/bile acid receptor), liver X receptor, fibroblast growth factor-19 and TGR5-mediated effects on intestinal glucose absorption and/or hepatic glucose metabolism, in addition to influences on peripheral insulin sensitivity, incretin effects and energy homeostasis.

CAUTIONS:

Colesevelam can increase triglyceride levels in patients with T2DM. Caution is therefore recommended in patients with triglyceride levels *>300 mg/dl (>3.4 mmol/l), and* colesevelam is contraindicated in patients with triglyceride levels *>500 mg/dl (>5.7 mmol/l) and in patients with* a history of hypertriglyceridaemia-induced pancreatitis.

Colesevelam has a high capacity for bile acid binding with a low potential for interfering with the absorption of other agents. However, patients taking levothyroxine, oral contraceptives or glyburide should take these agents at least 4 h before colesevelam to avoid any potential for impaired absorption. Use of colesevelam may also decrease the absorption of fat-soluble vitamins including A, D and E [21].

Fonseca V, et al. Diabetes Obes Metab. 2010 May; 12(5): 384ï 392.

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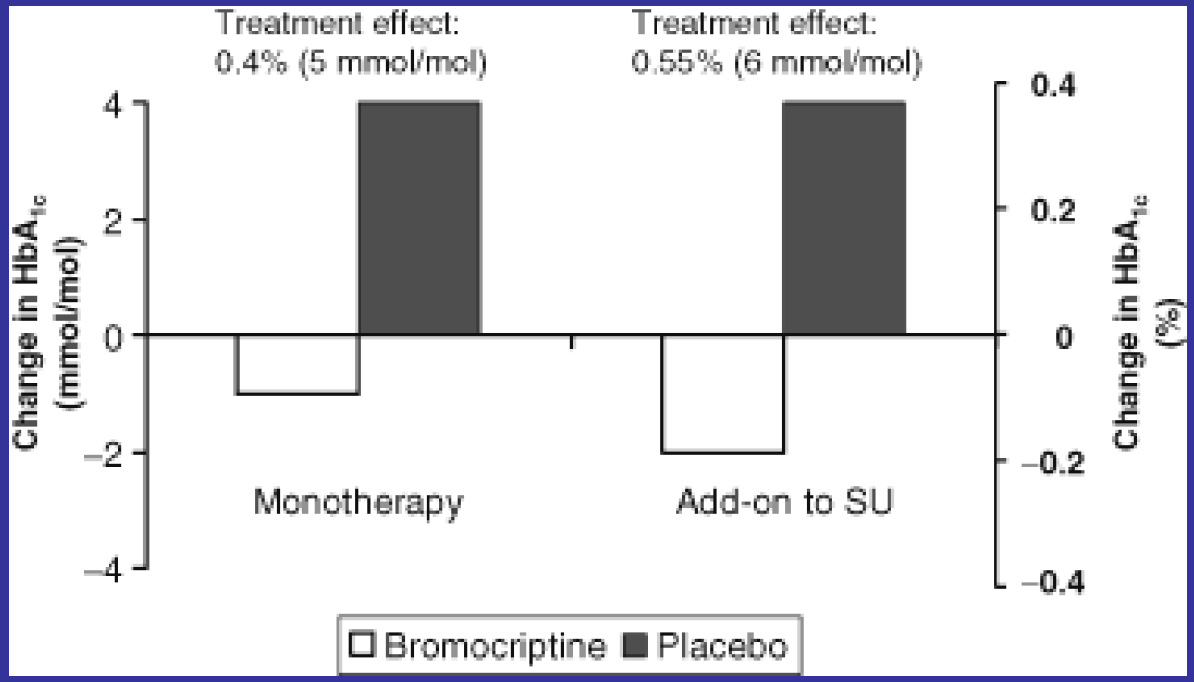
- Dopamine agonists
  - Bromocriptine-QR (Cycloset)

Bromocriptine-QR (Cycloset)

Dosing: Start with 0.8 mg (one tablet) within two hours of awakening in the AM. Increase weekly as tolerated to target dose of 1.6 to 4.8 mg upon awakening



Holt RIG, et al. Diabetes, Obesity and Metabolism 12: 1048–57, 2010

Bromocriptine-QR

Tolerability

Severe adverse events: placebo 14% vs. bromocriptine-QR 17%
Discontinuation due to adverse event: placebo 9% vs. bromocriptine-QR 22%
Nausea: placebo 7% vs. bromocriptine-QR 31%; generally transient, up to 2 weeks, but can reduce compliance or ability to titrate.
Orthostatic hypotension: placebo 0.8% vs. bromocriptine-QR 2.2%; particularly upon initiation or dose escalation. Use caution in patients taking anti-hypertensive medications. Assess orthostatic vital signs prior to initiation of Cycloset and periodically thereafter.
Psychosis: Bromocriptine may exacerbate psychotic disorders or reduce the effectiveness of drugs that treat psychosis; not reported w QR formulation to date.
Somnolence: placebo 1.3% vs. bromocriptine 4.3%, particularly when initiating therapy

Safety

Cardiovascular: event rate lower in those receiving bromocriptine-QR than placebo [1.8% vs. 3.2%: hazard ratio (HR) 0.60, confidence interval (CI) 0.35ï 0.96] in 1-year safety study.
Fibrosis: ergot-derived dopamine receptor agonists have been associated with pulmonary, retroperitoneal and pericardial fibrotic reactions. For theoretical reasons this may be less likely to occur with bromocriptine-QR
Drug interactions: As an ergot-derived dopamine receptor agonist which is extensively metabolized via CYP-3A4, caution should be used in combination with other ergot-related drugs, dopamine receptor agonists or antagonists and strong inhibitors/agnoists/substrates of CYP3A4.

Holt RIG, et al. Diabetes, Obesity and Metabolism 12: 1048–57, 2010

Antihyperglycemic Agents in Type 2 Diabetes

Class	A1C Reduction	Hypo-glycemia	Weight Change	CVD Risk Factors	Dosing (times/day)	Diabetes Comorbidity Contraindications
Metformin	1.5	No	Neutral	Minimal	2	Kidney, liver
Insulin, Long-acting	1.5 - 2.5	Yes	Gain	TG	1, Injected	None
Insulin, Rapid-acting	1.5 - 2.5	Yes	Gain	TG	1-4, Injected	None
Sulfonylureas	1.5	Yes	Gain	None	1	Essentially none
Thiazolidinediones	0.5 - 1.4	No	Gain	Variable	1	CHF, liver
Repaglinide	1 - 1.5	Yes	Gain	None	3	Essentially none
Nateglinide	0.5 - 0.8	Rare	Gain	None	3	Essentially none
Alpha-glucosidase Inhibitors	0.5 - 0.8	No	Neutral	Minimal	3	Essentially none
Amylin-mimetics	0.5 – 0.9	No	Loss	With weight loss	3, Injected	None
GLP-1 R Agonists	0.5 - 1.0	No	Loss	With weight loss	2, Injected	Kidney
DPP-IV Inhibitor	0.6 - 0.8	No	Neutral	None	1	None
Bile acid sequestrant	0.5	No	Neutral	LDL	1-2	Severe TG's
Bromocriptine	0.5	No	Neutral	Minimal	1	Essentially none
Long-acting GLP-1 R Agonists	~1.5%	No	Loss	Yes	1 or <1	Essentially none

Adapted from: Nathan DM, et al. *Diabetes Care.* 2007;30:753-759; Nathan DM, et al. *Diabetes Care*. 2006; 29:1963-1972; Nathan DM, et al. *Diabetes Care.* 2008;31:173-175. ADA. *Diabetes Care.* 2008;31:S12-S54. WelChol PI. 1/2008; Cylcoset PI 5/2009; Victoza PI 2/2010.